

# Can We Improve the Criteria for Diagnosis of Allergic Bronchopulmonary Aspergillosis as an Endotype of Asthma?



Paul A. Greenberger, MD Chicago, Ill

Since the initial reports of allergic bronchopulmonary aspergillosis (ABPA) by Hinson et al<sup>1</sup> in 1952 in London and then in the United States by Patterson and Golbert<sup>2</sup> in 1968 in adults and Slavin et al<sup>3</sup> in 1970 in children, the diagnosis has been made by “pattern matching” with a collection of diagnostic criteria. The classical criteria include asthma, usually persistent, but may be in patients with intermittent asthma or even no apparent asthma, elevated total serum IgE concentration, immediate cutaneous reactivity, or *in vitro* laboratory result for anti-*Aspergillus fumigatus* IgE antibodies, a history of transient pulmonary infiltrates, typically in the upper lobes or middle lobe, peripheral blood eosinophilia, and proximal (central-inner two-third of the lung fields) bronchiectasis.<sup>4</sup> In patients with ABPA, the sputum is very tenacious, and when patients underwent bronchoscopy to evaluate unexplained pulmonary infiltrates and rule out lymphoma, the bronchoscopist would realize after 20 minutes of futility that the mucus was not being extracted as in other conditions. This teachable moment for pulmonologists helped lead to more identified cases of ABPA by chest physicians. In addition, the use of computed tomography (CT) scanning with high-resolution (thin-section interstitial lung disease) examination provided first-hand appreciation by radiologists of possible ABPA, whether by recognizing the proximal but not distal bronchiectasis, location and character of and at times, high attenuation bronchial mucus, or presence of “tree-in-bud” findings. Some patients were referred to or diagnosed by allergist-immunologists because of unexplained peripheral eosinophilia, worsening of asthma, acute or chronic cough, or following up on a patient who described expectorating a “thick plug,” “worm,” or “pearl.” Others were from considering the posttest probability of ABPA in patients with positive immediate skin test results to *Aspergillus* species. Unrecognized and untreated infiltrates have caused bronchiectasis in the areas of roentgenographic infiltrates and subsequent reduction of respiratory status and pulmonary physiology. This led to the

importance of astute physicians and other health care professionals considering ABPA in patients with asthma and also in cystic fibrosis (CF), where bronchiectasis typically had preceded the diagnosis of ABPA. In patients with CF, the bronchiectasis was proximal and distal. To help in the diagnosis and treatment in patients with asthma, ABPA was organized into 5 stages: I: Acute, II: Remission, III: Exacerbation, IV: Corticosteroid-dependent asthma, and V: End-stage fibrotic and/or cavitary.<sup>5</sup> ABPA has been described in patients without bronchiectasis and designated as “sero-positive.”<sup>6</sup> Such patients could develop bronchiectasis over time when future pulmonary infiltrates with eosinophilia occurred and were not treated. For some patients, aerobiologic conditions were relevant as it was reported that in a 5-year period, 38 of 49 (77.5%) new pulmonary infiltrates with rise in total serum IgE concentration, compatible with an exacerbation of ABPA, occurred in the months June to November, when outdoor mold recoveries were highest in Chicago, Ill.<sup>7</sup>

Important individual criteria have high utility in discrimination of patients with ABPA from patients with persistent asthma and immediate sensitivity to *A fumigatus* (a form of fungal asthma). One useful finding, almost pathognomonic finding in patients with persistent asthma, is high attenuation mucus characteristically visualized on CT or magnetic resonance imaging scanning of the lungs.<sup>8,9</sup> A second is that sera from patients with ABPA have greatly increased quantities of anti-*A fumigatus* IgE, IgG, and IgA antibodies as compared with patients with asthma (without ABPA) who were 3+ or 4+ positive on immediate skin testing to *A fumigatus* or a mix of *Aspergillus* species.<sup>10</sup> This determination reminds us that the usual commercial *in vitro* measurement for anti-*A fumigatus* IgE reports sera as compared with nonatopic controls not discrimination with sera from *A fumigatus*-positive patients with asthma without ABPA. It also is a reminder that in ABPA, the isotypic antibody responses are very large indeed as an example of an endotype of asthma with its particular presentations, pathophysiology, and treatments.

In this issue, Saxena et al<sup>11</sup> report results from a latent class analysis testing for modifications of the initial Patterson and Golbert criteria and those of the International Society for Human & Animal Mycology (ISHAM) by focusing on patients from a single, pulmonary center with persistent asthma who were younger than 66 years and who had not received oral corticosteroids for 3 weeks in the past 3 months. Some 543 patients were assessed for ABPA using the 1977 Patterson and Golbert and ISHAM criteria.<sup>11</sup> With both systems, the prevalence of APBA was 16%. Because of modifications to the ISHAM criteria, such as reducing the total IgE concentration from more than 1000 IU/mL to 500 IU/mL, which is similar to the more

Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Ill

This study was supported by the Ernest S. Bazley Foundation grants to Northwestern Memorial Hospital and Northwestern University.

Conflicts of interest: P. A. Greenberger has received royalties from Wolters Kluwer and is a consultant for Allergy Therapeutics.

Received for publication October 6, 2020; accepted for publication October 9, 2020.

Corresponding author: Paul A. Greenberger, MD, Division of Allergy and Immunology, 211 E. Ontario St, # 1000, Chicago, IL 60611. E-mail: [p-greenberger@northwestern.edu](mailto:p-greenberger@northwestern.edu).

J Allergy Clin Immunol Pract 2021;9:336-7.  
2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology  
<https://doi.org/10.1016/j.jaip.2020.10.011>

than 417 IU/mL of Patterson and Golbert, there was improved identification of cases with the modified ISHAM criteria.<sup>11</sup> The study explored and concluded that removing skin testing completely and adding CT findings and *in vitro* measurement of anti-*A fumigatus* IgE antibodies would improve utility of the ISHAM criteria. Is it time to make these changes? Regarding removal of skin test results, many allergist-immunologists skin test nearly all new patients with asthma and then can recommend what avoidance measures are advisable regarding mold allergy and whether there should be further workup to rule in or rule out ABPA. In this setting, the use of a highly sensitive test, such as immediate skin test reactivity to an *Aspergillus* mix or *A fumigatus*, helps to exclude ABPA if the test result is negative (SNOUT—a highly SeNsitive test, if result is negative, rules OUT the condition). For physicians, especially pulmonologists, who suspect ABPA but do not perform skin testing, *in vitro* measurement of anti-*A fumigatus* IgE would be reasonable. However, my opinion is that the criteria should not be too restrictive because of these differences in practices. Many patients with suspected ABPA will undergo high-resolution CT scanning in the workup. The caveat is that if there is no current pulmonary infiltrate or if the patient has no bronchiectasis, one must acknowledge that the patient could have seropositive ABPA.

With reports of reduced exacerbations of asthma and some reductions in inflammatory markers in patients with ABPA who have been treated with biologics, such as with mepolizumab,<sup>12</sup> benralizumab,<sup>13</sup> omalizumab,<sup>14</sup> and dupilumab,<sup>15</sup> and hopefully, in the near future with novel inhaled antifungal agents, it remains important to identify patients with ABPA and provide improved therapies to avoid new or additional areas of bronchiectasis, scarring of lung parenchyma, and loss of lung function.

## REFERENCES

- Hinson KFW, Moon AJ, Plummer NS. Broncho-pulmonary aspergillosis: a review and report of eight new cases. *Thorax* 1952;7:317-33.
- Patterson R, Golbert TM. Hypersensitivity disease of the lung. *Univ Mich Med Cent J* 1968;34:8-11.
- Slavin RG, Laird TS, Cherry JD. Allergic bronchopulmonary aspergillosis in a child. *J Pediatr* 1970;76:416-21.
- Greenberger PA, Bush RK, Demain JG, Luong A, Slavin RG, Knutsen AP. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract* 2014;2:703-8.
- Greenberger PA, Patterson R. Allergic bronchopulmonary aspergillosis: model of bronchopulmonary disease with defined serologic, radiologic, pathologic and clinical findings from asthma to fatal destructive lung disease. *Chest* 1987;91:165S-71S.
- Greenberger PA, Miller TP, Roberts M, Smith LL. Allergic bronchopulmonary aspergillosis in patients with and without bronchiectasis. *Ann Allergy* 1993;70:333-8.
- Radin RC, Greenberger PA, Patterson R, Ghory A. Mould counts and exacerbations of allergic bronchopulmonary aspergillosis. *Clin Allergy* 1983;13:271-5.
- Phuyal S, Garg MK, Agarwal R, Gupta P, Chakrabarti A, Sandhu MS, et al. High-attenuation mucus impaction in patients with allergic bronchopulmonary aspergillosis: objective criteria on high-resolution computed tomography and correlation with serologic parameters. *Curr Probl Diagn Radiol* 2016;45:168-70.
- Sodhi KS, Gupta P, Shrivastav A, Saxena AK, Mathew JL, Singh M, et al. Evaluation of 3 T lung magnetic resonance imaging in children with allergic bronchopulmonary aspergillosis: pilot study. *Eur J Radiol* 2019;111:88-92.
- Greenberger PA, Patterson R. Application of enzyme-linked immunosorbent assay (ELISA) in diagnosis of allergic bronchopulmonary aspergillosis. *J Lab Clin Med* 1982;99:288-93.
- Saxena P, Choudhary H, Muthu V, Singh Sehgal I, Dhooria S, Thurai Prasad K, et al. Which are the optimal criteria for the diagnosis of allergic bronchopulmonary aspergillosis? A latent class analysis. *J Allergy Clin Immunol Pract* 2021;9:328-35.
- Schleich F, Vaia E-S, Pilette C, Vandenplas O, Halloy J-L, Michils A, et al. Mepolizumab for allergic bronchopulmonary aspergillosis: report of 20 cases from the Belgian Severe Asthma Registry and review of the literature. *J Allergy Clin Immunol Pract* 2020;8:2412-3.
- Soeda S, Kono Y, Tsuzuki R, Yamawaki S, Katsube O, To M, et al. Allergic bronchopulmonary aspergillosis successfully treated with benralizumab. *J Allergy Clin Immunol Pract* 2019;7:1633-5.
- Li J-X, Fan L-C, Li M-H, Cao W-J, Xu J-F. Beneficial effects of omalizumab therapy in allergic bronchopulmonary aspergillosis: a synthesis review of published literature. *Respir Med* 2017;122:33-42.
- Ramonell RP, Lee FE-H, Swenson C, Kuruvilla M. Dupilumab treatment for allergic bronchopulmonary aspergillosis: a case series. *J Allergy Clin Immunol Pract* 2020;8:742-3.